rejection...." Applicants wish to point out, however, that the Examiner has essentially used the same arguments and citations verbatim that were set forth in the previous Office Action. The claims were amended in Applicants' December 10, 1999 Amendment and Response to specifically recite that the lysostaphin analog must be recombinant; however, the Examiner had already cited in the previous Office Action the reference of Oldham, et al. and its teaching of recombinant lysostaphin. Nothing new with regard to the reference has been set forth in the present Office Action, nor have any new references been cited as teaching the use of recombinant lysostaphin. The claims added in the December 10, 1999 Amendment and Response were introduced as direct replacements for original claims that were canceled via the same Amendment. No "new" subject matter, i.e., matter requiring further search or raising new issues, is recited in the claims added in Applicants' last response.

Furthermore, the only ground of rejection which can remotely be said to be "new" is that set forth in section 6 on page 7 of the present Action. The stated ground of the rejection is that the present claims recite particular dosage ranges and that any differences between the instantly claimed ranges and those disclosed in the cited prior art would be minor in nature. Regardless of whether or not this assertion has any merit, the original claims recited the same particular dosage ranges as do the present claims and, thus, the recitation of said ranges in the latter cannot be said to constitute amendments necessitating new grounds of rejection. Applicants respectfully request that

the Examiner withdraw the finality of the rejection and treat the present response as if it were a response to a non-final action.

Applicants acknowledge the Examiner's withdrawal of the previous indefiniteness and anticipation rejections.

In fulfillment of their duty of candor, Applicants wish to bring to the Examiner's attention related, coassigned Application Serial No. 09/140,732 of Climo, et al., which issued February 22, 2000 as Patent No. 6,028,051. A copy of the patent is provided herewith. Entry and consideration of this reference is respectfully requested.

Claims 4, 5, 28 and 29 have been rejected under 35 U.S.C. §103(a) as obvious over the reference of Zygmunt or Stark or Goldberg, each taken in view of Oldham. Applicants assert that regardless of any routes of administration, dosages and/or utilities of lysostaphin disclosed by the primary references, one would have been taught away from the instantly claimed subject matter by the teaching of Oldham.

The Examiner cites Oldham because it "teaches that lysostaphin can be produced recombinantly and demonstrates that recombinant lysostaphin ... is effective against *S. Aureus* in mammary tissue," asserting that reliance on Oldham is appropriate because "it is well established in the art that recombinant way of production of proteins is easier and more effective than non-recombinant methods (such as organic synthesis or purification)." In the first place, the Examiner has provided no support for these assertions. In any case, reliance on such assertions ignores specific teachings of Oldham away from the use of

recombinant lysostaphin that render such considerations inconsequential.

As also acknowledged by the Examiner, Oldham is confined to a localized treatment, infusion of bovine mammary glands to treat mastitis. On page 4182 of the cited Oldham reference, the authors even contrast this particular situation with studies they previously reported involving systemic administration of recombinant lysostaphin ("rLYS" in the reference). Oldham, et al. disclose that "rLYS is highly immunogenic when administered to some species parenterally in adjuvant" and, then, in contrast, "intramammary administration to the bovine ... were relatively nonimmunogenic." Applicants wish to emphasize that one of ordinary skill in the art would instantly recognize that a highly immunogenic protein is eminently unsuitable for systemic use, i.e., the use ascribed to the present invention.

Oldham, et al. further disclose in detail, beginning on page 4180, the unusual circumstances involving mastitis treatment, the effect of milk on rLYS activity and the possible reasons for this effect. In fact, in the right-hand column of page 4180, the authors state that understanding the basis for reduced activity of rLYS in their system is essential in order to target proper therapeutic formulations.

Further along these lines, Oldham, et al. disclose (page 4180, right-hand column) the desirability of administering multiple infusions of rLYS to maintain minimal bactericidal activity within the milk and on page 4181, left-hand column, that

while rLYS may be effective at eliminating bacteria present in milk, it is not sufficient to elicit cures.

Implicit in the Examiner's stated grounds of rejection is the suggestion that the Oldham model is appropriate for predicting the efficacy of *in vivo* systemic administration in treating infection and diseases caused thereby; this constitutes an inappropriate assessment of the significance of the disclosure of Oldham. Applicants agree with the Examiner that perfect predictability is not required for obviousness, but wish to point out that there must be some basis for acquiring belief in the viability of a proposed solution. However, in merely considering that Oldham, et al. disclose rLYS and not assessing what Oldham specifically teaches with respect to the protein, the Examiner has ignored knowledge in the field that would actually dissuade one of ordinary skill in the art from applying the Oldham model to a solution of the problem addressed by Applicants' invention.

Oldham teaches that rLYS is highly immunogenic in systemic administration; this alone is sufficient to teach away from the instant invention. Applicants wish further to point out that the very method identified by Oldham as posing the problems with immunogenicity, parenteral administration in Freund's adjuvant, is precisely the method taught by the primary references cited by the Examiner (see, e.g., Zygmunt, page 237). Thus, whatever the references may or may not teach about naturally occurring lysostaphin, it is clear that the teaching in the art with regard to recombinant lysostaphin is that it is immunogenic, certainly when administered systemically, and the data suggest that, even

if it is administered locally, curing of infection does not ensue in a high percentage of cases.

As demonstrated by the reference cited by the Examiner, published prior to Applicants' filing date, the only therapeutic use suggested for recombinant lysostaphin appears to be infusion in the treatment of mastitis. As set forth above, the cited reference of Oldham, et al. specifically presents issues distinct from those embraced by the subject matter of the instant claims.

Clams 32 and 35 have been rejected under 35 U.S.C. §103(a) as being obvious over the same combinations of references, and for the same reasons applied to claims 4, 5, 28 and 29, and further in view of the disclosure of Dixon. The Examiner's basis for invoking Dixon is the assertion that Dixon teaches "that it is preferable to use lysostaphin in combination with other antimicrobials because a single dose usage of lysostaphin reduces dangers of hypersensitivity reaction." This rejection, too, involves an inappropriate reading of the cited disclosure and should be withdrawn.

As the Examiner acknowledges, Zygmunt teaches sequential administration of antimicrobials, i.e., lysostaphin followed by "another antibiotic." Applicants further note that, other than Dixon and Zygmunt, the cited references are silent regarding combinatorial therapy and, in fact, focus on the administration of lysostaphin alone, warning of the complications associated with such, whether the lysostaphin is natural or recombinant. The specific strategy behind the Zygmunt teaching of initial administration of lysostaphin followed by an antibiotic is the

idea that the lysostaphin will reduce high bacterial titers in emergency situations, thereby enhancing efficacy of subsequently administered conventional antibiotics. Not only does such teaching not render the instant invention obvious, but it teaches away from the invention.

Dixon, like Zygmunt, teaches the sequential administration of lysostaphin first and then a conventional antibiotic. The Examiner acknowledges that the primary references do not teach combined use of lysostaphin and another antimicrobial but uses terms such as "combination therapy," "combined use," and "in combination" interchangeably, without distinguishing between the various ways of practicing combinatorial therapy, thus muddling the clear distinction between the instantly claimed invention and that of the cited disclosure.

The instant claims require that lysostaphin be combined with, and administered together with, a companion antibiotic. However, this is contrary to the strategies employed by Dixon and Zygmunt, who specifically envisioned sequential administration, first of a single dose of lysostaphin, in the hope of initially blunting the infection while avoiding adverse reactions and resistance (i.e., reducing the danger of hypersensitivity), and secondly of a companion antibiotic. The teachings of Dixon and Zygmunt are clearly not that of the instant invention, nor are they suggestive thereof.

With regard to the issue of analogues, the Examiner appears to be maintaining the obviousness of such on the basis of Applicants' own disclosure defining the metes and bounds of the

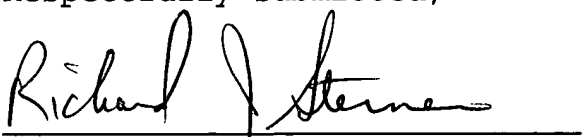
term "analogue," surely an inappropriate ground of rejection. In any case, in view of the arguments set forth above, whether or not it can be said that lysostaphin analogues follow from lysostaphin itself, it cannot be said that lysostaphin itself follows as the active ingredient to be employed in the instantly claimed invention. In other words, lysostaphin itself, and appropriate pharmaceutical compositions comprising it, are not obvious in the context of the present invention, and, therefore, analogues of lysostaphin certainly cannot be considered obvious in the present context.

In view of the taught immunogenicity of recombinant lysostaphin when administered systemically, the acknowledged inapplicability of the mastitis model in predicting efficacy for other treatments and the specific teaching of sequential administration of active ingredients in those cited references disclosing combinatorial therapy, the instantly claimed invention is free of the cited prior art. Reconsideration and allowance of pending claims 4, 5, 28, 29 and 32-55 are respectfully requested. Should any other matters require attention prior to allowance of the application, it is requested that the Examiner contact the undersigned.

No fee should be due in connection with this communication. However, should it be determined that a fee is required for any reason, The Assistant Commissioner is authorized to charge it to Deposit Account No. 23-1703.

Dated: June 13, 2000

Respectfully submitted,



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Enclosures